MEMORANDUM

BRISTOL LABORATORIES

UNIT OF BRISTOL-MYERS COMPANY

FROM J. Lederberg

TO J. Lein

C.C.

DATE March 21, 1955

SUBJECT New Antibiotics Screening Program - ~~Consultantship Arrangement~~

Hi Joe,

Thanks very much for sending me the account of your general screening program. I can see I have quite a job cut out ahead of me if you really expect me to bring up anything that might lead to any substantial improvement. I just wanted to say now that I have listened to your account once and before I go into very much detail I would like a few more days in which to mull things over as I'm sure you'd like to have more than an off-the-cuff response. I might say that my general reaction was extremely favorable, I might say almost enthusiastic. In fact, I would almost be led to think that the one outfit, which apparently has thought to provide itself with outside genetic consultation, is perhaps already so well oriented with the desirability of it and with the fundamental approaches that might be added there that it may not need it. I'll do my best to earn my way with you, Joe, but I, frankly, don't expect that I will be able to add a great deal to what you have already laid out. If I can think of particular things or generalities I will make notes on them and record them as they go along and I undoubtedly will have somewhat more detailed comments on this last, particular record.

I was quite struck however during listening to your last record that practically every comment that I began to formulate in my own mind as you went along merely anticipated what you were going to go into yourself. I do agree that the type of approach which Kilner first made use of -- I might say I was a little surprised that he had the initiative to go into it as far as he did and then disappointed that he didn't carry it a little bit further, but it would seem to me that that would indeed be a highly promising type of affair but the important point will be to try to establish methods that are as efficient as possible for the detection of the widest variety of the accumulating type of variant.

I approach this whole question of antibiotic screening with the question in the back of my mind, "just what are antibiotics?" and I was very pleased that you yourself brought that up. I can see that you have been giving, of course, your concentrated attention to this whole field for a number of years whereas my interest in it so far has been highly casual and it may take quite a bit of time before I can catch up with you in any particular area, not to mention the whole concept of what you are doing. Your report did give me a very clear idea of what your general approach is and I don't think there will be any general statements that will need to be amplified although I may want to go into some of the very particular details.

One comment about this technique of going about things, you will probably get from me a combination of written and spoken material. When there is something that needs to be outlined, the structure of which has to be seen at once, it is, of course, much better on paper than it is on a dictation. On the other hand, I do think that using the records provides a much more intimate touch and enables one to digress somewhat on things that are too fleeting sometimes to put down on paper and I think that with

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a little practice we may find that a combination of the spoken and the written word will be much more effective.

Technically, your record is, I think, quite satisfactory although I think it could be improved slightly if you would speak more loudly, or rather speak more closely to the microphone itself. If you make some records of your own you might compare them with the one that I have here. Otherwise there may be something defective with your machine because I know it is capable of producing a higher fidelity than the record that I have received, although it was quite adequate. The recording that I am sending you now is not, to use that unhappy metaphore, up-to-scratch itself because we have been using in the department resurfaced records, that is, once the records have been used once they can be sent to the service outlet and have a new surface put on but these records are often not quite as smooth as the new ones. I think you'll have no trouble whatever in getting my language here however. I think then that with the simple comment that off-hand I did not find very much that one could obviously improve upon and that I want to let the matter run around in my head for awhile, so to speak, that I won't say anymore at the present time so this is essentially an acknowledgement of your first assignment and I want to tell you that I am giving it as much consideration as I have time for. It happens to be a rather busy couple of weeks because I have a meeting coming up in Washington which however will be over with by the end of the week and I will be able to give closer immediate attention to this stuff.

There is one particular thing that I would like to ask you about on the experimental program and that is that you mentioned that you are using Actinomyces which have no evident activity to start with. Since there are probably two functions which one has to consider for the efficiency of antibiotic production by an Actinomycete I wonder if this is necessarily the only choice that might be made. The two functions that I have in mind are first the metabolic capability of accumulating a given metabolite which, for the purposes of agreement with you on the general function of antibiotics is what I will consider a potential antibiotic to be. The other is the ability to excrete this into the medium in very large amounts. And it seems to me conceivable that the processes of selection by means of which the most efficient producers of antibiotics have been obtained might have not only some special attribute with regard to that specific antibiotic but also the more generalized one of high incidences of metabolic metabolite accumulation and excretion into the medium. Now to put it in other temrs, the point of view of the artificial selection which one uses on Streptomyces strains, some of the so-to-speak adaptation of the strain might be highly specific and directed toward that particular antibiotic and in fact might be maladapted with respect to any other metabolite. On the other hand, some of that so-to-speak adaptation might be more generalized. What I mean in more concrete terms is that conceivably or, at least as an alternative possibility, one might for such a screening program use not an organism with an indifferent capacity to produce any antibiotic but one which has already been selected for a moderate-to-high capacity to produce one specific antibiotic already. Then by using a test organism which was resistant to that first antibiotic, one would be in an advantageous procedure for selecting alternatives. This may have a deeper meaning than the one I have already presented. There has been, for example, considerable attention given to the possibility of finding derivative streptomycins which would not show such strong

cross-resistance to streptomycin itself and you face the same situation as between tetracycline and its chlorinated and hydroxylated derivatives. And I have wondered it it would not be a feasible approach to look for the specific modification, the specific biological modification of these metabolites as a starting point for new antibiotics, namely, by using good high-producing strains for a given antibiotic in attempting to produce derivatives from it which would be effective against bacterial mutants which were resistant against the original. Just to be sure that I have made myself clear, what I would mean is that one would take the highest producing strain now available or perhaps nearly the highest, say for streptomycin, and look for variants of this strain which will have some activity against some of a number of streptomycin-resistant mutants, let us say of B. subtilis or of anything else. There is the possibility that one would be getting a specific direction of selection for antibiotics by finding specific metabolic modifications of streptomycin which would in some way be able to surmount the barrier of genetic resistance. By itself, this would of course by a very considerable contribution.

Well, you will hear directly from me again as soon as I have had some better opportunity to assimilate what I have here. I did want to give that particular suggestion just as a test sample to see if that is the kind of thing that you are looking for because I am still so struck by the adequacy of the approach that you have already given that I hardly know in what way I will be able to contribute. Well, so long now.

Josh

JL:mjl